REMARKS

Claims 1, 3 and 4 have been amended. Claims 2, 5 and 6 have been canceled. Claims 1, 3, 4, and 7-47 are pending. Claims 8-47 are withdrawn.

Applicant acknowledges the Examiner's withdrawal of the previous rejections under 35 U.S.C. §102 and/or §103, as anticipated by Rosen et al., or by Ball et al., or by Arystarkhova et al., or over Arystarkhova et al. in view of Rosen et al., Schwinger et al., Mohraz et al., Bost et al., and Bendayan et al. in view of Applicant's amendment to the claims.

Claims 1 and 3 were objected to because they failed to recite the proper SEQIDNO when referring to Applicant's polypeptide sequence. Applicant has inserted the proper sequence identifiers and respectfully requests that the rejection be withdrawn as moot.

Claims 1-3, 5 and 7 were rejected under 35 U.S.C. § 102(b) as being anticipated by Arystarkhova *et al.* (*J. Biol. Chem.* 1992 Jul 5;267(19):13694-701) as evidenced by Bost *et al.* (*Immunol. Invest.* 1988; 17:577-586) and Bendayan *et al.* (*J. Histochem. Cytochem.* 1995; 43:881-886), as recited in the previous Office Action. The Examiner alleges that "Arystarkhova teaches that the VG4 antibody binds an epitope composed primarily of contiguous amino acids QAATEEEPQNDNL of pig α1 NaK ATPase, wherein the 'crucial' EEEP residues are conserved between rat α1 and porcine α1 NaK ATPase AND Arystarkhova further teaches that VG4 does indeed bind rat α1 NaK ATPase with an affinity slightly lower than its affinity for porcine α1 NaK ATPase." Applicant respectfully traverses this rejection.

In his rejection, the Examiner consistently points out that Arystarkhova *et al.* determined through epitope mapping, that the VG4 antibody bound to residues between the H1-H2 regions of the NaK ATPase. The Examiner goes on to state that Arystarkhova *et al.* deduce that amino acid residues 114-117 of the NaK ATPase seem to be crucial for their antibody affinity. Thus, the Examiner makes the argument that because the VG4 antibody binds residues 114-117 of the NaK ATPase, and these four residues are also found in Applicant's target peptide SEQ ID NO:1, one of ordinary skill in the art would understand that the VG4 antibody, and Applicant's claimed antibody, must have the same structure, and the same function, or, in the alternative, that is highly possible or probable that the VG4 antibody has the same structure or function as Applicant's claimed antibody.

To scientifically assess whether two antibodies are identical, two fundamental criteria must be applied: a) the antigen used to make the antibody must have identical composition; b) the identical antibodies must have the identical biological function. These two principles can not be separated during the professional evaluation. Furthermore, the non-specific cross reactivity of an antibody is not equivalent to the biological function of an antibody.

Applicant submits that Arystarkhova et al., teach the following:

i) VG4 was made against the entire (Na^++K^+)-ATPase isolated from pig kidney outer medulla (Ovchinnikov et al., FEB, 1988, 227:230-234, in Materials and Methods section on page 230);

ii) VG4 recognized native pig and rat kidney (Na^++K^+)-ATPase, but failed to detect SDS-denatured enzyme on Western blots even at high concentrations of VG4 (page 13696 of Arystarkhova et al paper);

iii) Arystarkhova et al. has no idea where are the antigenic sites are located on the (Na^++K^+)-ATPase. They clearly indicate that "The most likely targets for VG4 binding are short junctions between H1-H2 or H3 and H4 transmembrane rods; a

small loop connecting H5-H6; or uncertain portions of the C terminus following H7 or H8" (page 13696 of their J Biol Chem paper);

iv) VG4 inhibits (Na^++K^+)-ATPase activity "up to 50%" as shown in Figure 9 of their paper.

The fundamental differences between VG-4 and Jianye-2 antibody are provided in Table I below.

Table I. Fundamental differences between VG4 and Jianye-2

Antibody Name	Antigen	Binding Specificity	Biological Activity
VG4	Entire (Na^++K^+)-ATPase including α and β subunits isolated from pig kidney.	a) No specificity, b) Only binds to native pig and rat (Na^++K^+)-ATPase, c) Failed to detect denatured enzyme and SEQ ID NO: 1 site even at high concentrations.	Inhibits enzyme activity up to 50%.
Jianye-2	RSATEEEPPNDD peptide or SEQ ID NO: 1	Specifically binds to both native and denatured enzyme at the specific RSATEEEPPNDD site.	a) Activates enzyme, b) no inhibition on the (Na^++K^+)-ATPase, c) Increases intracellular Ca and cardiac contraction.

The Examiner bases his argument on the assumption that antibody epitope binding is determinative of the structure of an antibody, which is not true. Where there may be sequence homology at the actual binding site, to the Applicant's knowledge, while no one has ever been able to completely predict the function of a protein by its sequence (structure), certain inferences can be made. The opposite, however, is not the case. One cannot predict the complete sequence (structure) of a protein by its function. Variant protein sequences can have the same physiological function.

Applicant also invites the Examiner to review Applicant's Declaration under 37 C.F.R §1.132, attached herewith. In the Declaration, Applicant provides more recent experimental data which support Applicant's claims that the claimed antibodies to SEQIDNO:1 have binding specificity and increase catalytic activity to the $(Na^+ + K^+)$-ATPase enzyme (Attachment A).

Moreover, the Examiner ignores two key factual differences between Applicant's antibody and the VG4 antibody. First, as stated above, the VG4 antibody was not made to SEQID NO:1, it was made to a tryptic digest of the NaK ATPase. This means VG4 was made to an unknown peptide fragment of indeterminate length, encompassed within the NaK ATPase, which could include the sequence between the H1 and H2 regions identified on Fig. 7A of Arystarkhova *et al.* This is not the same sequence as SEQIDNO:1 as claimed by Applicant. Just because the two peptides have the same four amino acids in their internal sequence homology, one cannot conclude scientifically, that the two antibodies have the same structure. Applicant's antibody was generated in rabbits and purified by affinity column. VG4 is one of a set of 11 monoclonal antibodies made to purified whole NaK ATPase from pig kidney. The methods of creation and antibody target (antigen) sequences are different, so that the antibodies cannot possibly have the same sequence or structure.

Second, there is no teaching or suggestion, that the antibodies taught in Arystarkhova *et al.* have the same positive inotropic effects in cardiac myocytes, as Applicant's claimed antibodies do. The Examiner argues that because the two antibodies have affinity for the same four amino acid site, they can be assumed to have the same effect, based on the secondary references cited. However, this argument is contrary to the teachings of Arystarkhova *et al.* At page 13699, it states:

> Since the Hl-H2 loop has been implicated in ouabain binding, the obvious question is whether VG4 and ouabain compete for the same site. [3H]Ouabain binding, after preincubation with VG4 or control IgG, was investigated under two different ligand conditions that are known to support binding (25). In both cases, VG, led to significant enhancement of bound radioactivity. In the presence of Na+, Mg2+ and 3 mM ATP binding was 196 +/- 29% of control *(n* = 4); in the same conditions but with only 0.1 mM ATP binding was 215 k 16% of control *(n* = 2). The decrease of ATP concentration from 3 to 0.1 mM did not affect the total amount of [3H] ouabain binding. In the presence of Mg2+ and Pi the binding in the presence of VG4 was 193 +/- 47% of control *(n* = 6). Similar results were obtained in different experiments with concentrations of [3H]ouabain of 10^{-7}-10^{-6} M.
>
> The [3H]ouabain data <u>were surprising,</u> not only because an increase in binding was seen instead of the predicted decrease, but also because there appeared to be an increase beyond what was ostensibly saturating...(emphasis added)

At page 13701, first column, antibody effects are discussed. In the second paragraph, Arystarkhova *et al.* state:

> When preincubated with purified Na,K-ATPase, VG4, enhanced the subsequent binding of [3H] ouabain. If we accept the premise that an antibody that binds to residues in a ligand binding site should sterically impede binding, the conclusion is that <u>the Hl-H2 loop is not likely to be part of the cardiac</u>

> glycoside binding site, unless the antibody binds to only a portion of the loop, leaving other portions still free to participate in ouabain binding. It is more likely that the Hl-H2 loop affects ouabain binding by conformational changes that are transmitted to other parts of the protein. A different antibody against the extracellular surface, M45-80, has been mapped to the region encompassing H3, H4, and the H3-H4 extracellular loop by its ability to react with expression products of different-length DNA fragments (39). Like VG4, it was capable of partially inhibiting enzyme activity, and it too enhanced ouabain binding, rather than blocking it (30). In theory, it should be possible to produce other antibodies to the same sites which will reduce cardiac glycoside binding by stabilizing a different conformation. (emphasis added)

Arystarkhova *et al.* actually teach that one of ordinary skill in the art could not predict what the binding of an antibody to the Na,K-ATPase would do to the enzyme's function. Furthermore, Arystarkhova *et al.* also teach that it should be possible to produce other antibodies to the same binding sites which have the opposite functions. Thus, to one of ordinary skill in the art, the fact that the prior art teaches that VG4 has binding affinity to the EEEP tetrapeptide sequence does not give any indication of whether the antibody would also increase positive inotropic activity in cardiac tissue.

With regard to Bost et al., they teach that HIV envelope protein crossreacts with human interleukin-2. Bost et al. do not teach that SEQ ID NO: 1 can be used as antigen to specifically generate Applicant's Jianye-2 antibody, nor do Bost et al. teach that Applicant's Jianye-2 antibody increases cardiac contraction. Applicant submits that crossactivity is not equivalent to antibody specificity. It means that the binding sites are similar enough in three dimensions that there is some binding with lower affinity. Therefore, the publication of Bost et al. does not provide any essential scientific basis for supporting the Examiner's assertion that the VG4 antibody has the same structure or function as Applicant's antibody.

Similarly, with regard to Bendayan et al., they teach possible immunocytochemical applications. Applicant respectfully states that this paper also does not provide any scientific basis for Examiner's rejection, because Applicant's invention is not directed to, and/or developed, using immunocytochemistry techniques. Bendayan et al. do not teach the fundamental issues regarding the specificity of an antigen or the biological function of an antibody. Moreover, Bendayan et al. teach away from the Examiner's assertion, because VG4 is not made against a large peptide sequence such as Applicant's SEQ ID NO: 1. As such, Bendayan et al. suggest that VG4 would be non-specific if the Examiner's assertion that VG4 is specific for the EEEP epitope is correct. Thus, Bendayan et al. do not provide any essential scientific rational for the Examiner's reliance on Arystarkhova *et al.*

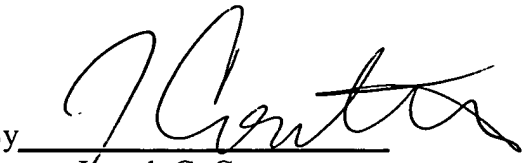
Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Although an applicant may be required to prove that the subject matter shown to be in the prior art does not possess characteristics relied upon, where an Examiner has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the functional limitation is an inherent characteristic of the prior art before the applicant can be put through this burdensome task. *Ex parte Skinner*, 2 USPQ2d 1788 (BPAI 1986).

Applicant submits that the prior art, taken as a whole, in the proper context, does not provide a reasonable scientific basis for the Examiner continue to assert that the VG4 antibody has the same structure and function as Applicant's claimed invention. As such, Arystarkhova *et al.*, as evidenced by Bost et al or Bendayan et al. does not teach each and every feature claimed by Applicants, and therefore cannot anticipate Applicant's invention. In view thereof, Applicant respectfully requests reconsideration and withdrawal of the instant rejection.

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all currently outstanding rejections, and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

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